Carcinogenesis vol.26 no.8 pp.1354–1359, 2005
doi:10.1093/carcin/bgi084
Advance Access publication March 31, 2005

Selected DNA repair polymorphisms and gastric cancer in Poland

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Impaired DNA repair capacity may adversely affect cancer risk, particularly in subjects exposed to DNA damaging carcinogens, as found in tobacco smoke, or among subjects deficient for protective factors, as found in fruits and vegetables. We studied tobacco use, fruit and vegetable intake, and common non-synonymous single nucleotide polymorphisms in four DNA repair genes in relation to gastric cancer risk, in a population-based, case–control study of 281 incident gastric cancer cases and 390 controls, in Warsaw, Poland. Multivariate logistic regression analysis was performed to calculate odds ratios (OR) and 95% confidence intervals (CI). Increased risks of gastric cancer were found for smokers (OR = 3.1, CI = 1.9–5.1 for pack-years ≥40 versus never smokers) and subjects with low fruit intake (OR = 2.2, CI = 1.3–3.6 for 1st versus 4th quartile); risk associated with vegetable intake was not statistically significant. Allele frequencies among the controls were consistent with those previously reported for the 5 polymorphisms studied: *XRCC1-Arg399Gln*, *XPD-Lys751Gln*, *MGMT-Ile143Val*, *Leu84Phe*, and *XRCC3-Thr241Met*. None of the studied polymorphisms were independently associated with gastric cancer risk. Smoking-associated risks, however, were greatest for carriers of the *XRCC1-399 ArgArg* genotype ($P_{interaction}$ = 0.004). Risks associated with low intake of fruits or vegetables tended to be modified by selected polymorphisms in *XRCC1*, *XPD* and *MGMT* ($P_{interaction}$ = 0.1–0.2). Risk modification was not found for the other repair polymorphisms. Selected DNA repair polymorphisms did not have independent effects on gastric cancer risk; however, they may modify smoking- and probably diet-related risks for this disease. These results need replication in larger epidemiological studies of gastric cancer.

Abbreviations: hME, homogeneous Mass Extend; MALDI-TOF MS, Assisted Laser Desorption Ionization-Time of Flight mass spectrometry; SNPs, single nucleotide polymorphisms; ROS, reactive oxygen species.

Introduction

Gastric cancer is one of the most common cancers and causes of cancer death in Poland (1); multiple environmental and lifestyle factors may play a role (2), including tobacco use (3,4), a diet poor in fresh fruits and vegetables or rich in salt (5,6), and *Helicobacter pylori* infection (7,8). Our interest is in gastric carcinogenesis due to exogenous factors that cause DNA damage and cancer (i.e. tobacco use) or prevent these effects (i.e. fruits and vegetables), and their interrelationship with potentially risk modifying polymorphic variants in DNA repair genes involved in the repair of exogenously-induced damage (9).

Multiple DNA repair pathways exist providing distinct but overlapping protection against DNA-damaging exposures. Enzymes in base excision repair (e.g. *XRCC1*), remove simple base modifications, such as single-strand breaks, non-bulky adducts, oxidative DNA damage, alkylation adducts and damage induced by ionizing radiation (10,11). Nucleotide excision repair enzymes (e.g. *XPD*/*ERCC2*) remove more complex, bulky lesions, often caused by environmental agents (e.g. polycyclic aromatic hydrocarbons and arylamines) or UV light (12,13); but also have been associated with the repair of oxidative stress (14,15). Mismatch repair removes mispaired bases, small loops, and small deletions generated during DNA replication and recombination (16,17). Methyl (and ethyl) transferase enzymes (e.g. *MGMT*/*AGT*) reverse rather than excise DNA damage, by transferring methyl (and ethyl) groups from the O6 position of guanine to a specific cysteine residue of the transferase enzyme (18,19). *XRCC3* acts in the homologous recombination repair of DNA double-strand breaks, generated by replication errors and endogenous and exogenous agents (20,21).

Since tobacco smoke is a rich source of reactive oxygen species (ROS) (22,23) and chemical carcinogens leading to DNA oxidative damage, PAH adducts, and alkylation adducts (24), the DNA repair pathways of ROS-induced double strand break repair, base excision repair, nucleotide excision repair, and alkyl (methyl and ethyl) transferase may be of particular importance to smoking-related gastric cancers. Since fruits and vegetables have high antioxidant properties and folate content, respectively, they can neutralize DNA-damaging free-radicals (25,26) and act as mediators of the methyl group transfer (27). These capacities may interact with DNA repair enzymes involved in base-excision, nucleotide excision, and double strand repair or with the *MGMT*/*AGT* alkyl transferases.

Polymorphic variants have been identified in a series of DNA repair genes (28–30) and some are suspected risk factors for gastric (i.e. *XRCC1*) (31–33) and other cancers (i.e. *XRCC1*, *XPD*, *XRCC3*) (21,24,34–39). To expand our understanding of the role DNA repair polymorphisms play in gastric carcinogenesis, we studied common non-synonymous single nucleotide polymorphisms (SNPs) in four DNA repair genes (i.e. *XRCC1*, *XPD*, *MGMT* and *XRCC3*), representing four

repair pathways, in relation to gastric cancer risk, in a population-based case-control study of gastric cancer in Warsaw, Poland.

Materials and methods

Study population

Design details of this population-based, case-control study of gastric cancer in Warsaw, Poland, are presented elsewhere (3). Briefly, residents of Warsaw, aged 21 to 79 years, who were newly diagnosed with a first gastric cancer (International Classification of Disease for Oncology: ICD-O 151 or ICD-O-2 C16) between March, 1994 and April, 1996, were eligible as cases. All cases were gastric adenocarcinoma and were identified through collaborating physicians in 22 hospitals and 8 private endoscopic units serving the study area and by regular reviews of the Cancer Registry files to ensure completeness of case ascertainment. Pathologic slides were obtained and reviewed in a standard fashion to confirm the diagnosis. Controls were frequency-matched to cases by sex and 5-year age groups, randomly selected from a computerized registry of Warsaw residents, which was updated monthly with nearly 100% registration completeness. Written informed consent was obtained from all participants and the study was approved by the Institutional Review Boards at the U.S. National Cancer Institute (NCI), Bethesda, Maryland and the Cancer Center and M. Sklodowska-Curie Institute of Oncology, Warsaw, Poland.

Data collection

Information was obtained through in-person interviews on demographic background, use of tobacco, alcohol and other beverages 2 years prior to interview, usual diet prior to 1990, lifetime occupational history, family history of cancer and personal history of selected medical conditions. Among eligible cases ($n = 515$) and controls ($n = 549$), successful interviews were conducted for 464 cases (90%; 324 direct interviews and 140 next-of-kin interviews, for deceased cases) and 480 (87%) controls. DNA was extracted from buffy coat isolated from a 30-ml blood sample or from pathology samples (98:2), resulting in 281 (61%) cases and 390 (81%) controls available for DNA-based analyses.

Genotype assay

Five DNA repair SNPs were studied: *XRCC1* codon *399* (Arg to Gln, base pair *28152 G* to *A*, exon 10, 19q13.2), *XPD* codon *751* (*Lys* to *Gln*, bp *35931 A* to *C*, exon 23, 19q13.2-3), *MGMT* codon *143* (*Ile* to *Val*, bp *74091 A* to *G*, exon 5, 10q24.33), *MGMT* codon *84* (*Leu* to *Phe*, bp *16282 C* to *T*, exon 3, 10q24.33) and *XRCC3* codon *241* (*Thr* to *Met*, bp *18067 C* to *T*, exon 7, 14q32.3). These SNPs were analyzed using Assisted Laser Desorption Ionization-Time of Flight mass spectrometry (MALDI-TOF MS) and homogeneous MassExtend (hME) chemistry (Sequenom Inc., San Diego, CA). Two MALDI-TOF/hME multiplex assays that included the five SNPs were optimized according to optimum assay partners, reaction terminator mixes and suitable primers both for genomic polymerase chain reaction (PCR) amplification of the SNP-containing sequences and DNA polymerase extension within the optimal mass range of 5000–8500 Da. Desalted PCR and extension oligonucleotides were obtained from Integrated DNA Technologies (Coralville, IA).

The hME procedure comprising amplification, dNTP removal and extension reactions was performed using the SpectroDesigner Software (Sequenom Inc.) for assay design. The PCR amplification cocktail was composed of 1× AmpliTaq Buffer, 2.5 mM $MgCl_2$, 115 μM dNTPs, 3–5 ng DNA template and 0.1 U of AmpliTaq Gold DNA polymerase. Forward and reverse primers were both at a 100 nM final concentration in a total reaction volume of 6.6 μl. PCR cycling was carried out in an MJ Research thermal cycler (Watertown, MA) with a 15-min denaturation step at 95°C, followed by 44 cycles of 20 s at 95°C, 30 s at 62°C, 1 min at 72°C and one last cycle of a 3 min hold at 72°C. Amplification was verified by running 1 μl of product on a 2% agarose gel. Non-incorporated dNTPs were removed by incubating the remaining amplification product at 37°C for 20 min in the presence of 0.5 U shrimp alkaline phosphatase, followed by 5 min at 85°C. Extension reactions were carried out on an MJ Research thermal cycler by adding 0.6 μM extension primer, 0.5 U Thermo Sequenase and a dideoxy/deoxy nucleotide mixture of ddATP, ddCTP, ddTTP and dGTP, at 50 μM each. The following extension cycling conditions were used: 2 min at 95°C, followed by 55 cycles of 5 s at 94°C, 5 s at 52°C and 5 s at 72°C. Extension products were desalted with SpectroClean Resin according to the manufacturer (Sequenom Inc.). The 384-element Matrix preloaded Spectro chips from Sequenom, Inc. (San Diego, CA) were spotted with ~15 nl of sample supernatant with a SpectroJet piezoelectric nanoplotter. MALDI-TOF mass spectrometry was carried out on a Bruker MALDI-TOF Biflex III instrument. Data acquisition and mass spectrometry, and genotyping were collected in an Sequenom SpectroTYPER RT workstation (Sequenom Inc., San Diego, CA).

Data analysis

We defined subjects who smoked at least one cigarette per day for 6 months or longer as smokers. Those who stopped smoking within the previous 2 years were considered current smokers. Cigarette pack-years were computed by multiplying packs of cigarettes smoked per day by the total years of smoking. For diet assessment, nutrient content of each food item was estimated using both US (40) and Polish food tables (41), with reference to original recipes for several unique Polish complex dishes (42). Gender-specific portion sizes were based on the POL-MONICA database (43) and DIETSYS portion sizes for food items that were unavailable in the POL-MONICA dataset (6).

Gastric cancer risk was estimated by calculating odds ratios (ORs) and 95% confidence intervals (CIs) using unconditional logistic regression. All analyses were adjusted for age, gender and smoking history (non-smoker, pack-years <40 and pack-years ≥ 40). Analyses involving dietary intake were additionally adjusted for total caloric intake from food (quartiles). Adjustments for additional suspected confounders, including education, first-degree family history of gastric cancer, red meat intake and years lived on a farm, led to no change in results and are not presented here. We performed trend tests for the three-level genotypes, cigarette use, and fruit and vegetable intake using logistic regression models based on the integer score (0,1,2). The effects of combined genes and exposures were examined by fitting a multiplicative model containing main effects and their cross-product terms, adjusted for confounders, with the inference based on the likelihood ratio statistic. All *P* values were two-sided. Individuals with missing values were excluded from specific analyses.

For genotype data, departure from Hardy–Weinberg equilibrium was assessed by comparing the expected genotype frequencies based on reported allele frequencies to the observed genotype frequencies. We estimated *MGMT* haplotypes defined by the codon *143* and *84* variants using HaploScore (44) and SAS/Genetics (45). Assessment of gastric cancer risk by haplotype for the two markers provides similar results to the individual genotype findings, and are not presented here.

Results

Distributions of study cases and controls were similar with respect to the matching factors of age (12%, <50 years; 17%, 50–59 years; 39%, 60–69 years; and 32%, ≥70 years) and gender (66% males and 34% females). Cases tended to be more likely to have had a first-degree family history of gastric cancer (13% versus 4%, $Px^2 = 0.2$) and had lower education (20% versus 31% of controls completed college, $Px^2 = 0.003$). Similar demographic and lifestyle factors were observed among cases and controls with and without DNA samples (e.g. age, gender, education, smoking and intake of fruits and vegetables ($Px^2 > 0.05$). Exclusion of data from subjects with DNA derived from tissue (2%) did not affect the results (data not shown).

In the case-control group for genotype analyses, gastric cancer risks increased with increasing cigarette use, rising to a 3-fold risk among those who smoked ≥40 pack-years (OR = 3.1, 95% CI = 1.9–5.1; $P_{trend} < 0.0001$; Table I). Excess risk was found for both former smokers and current smokers (data not shown). Lower intake of fruits (1st versus 4th quartile) was also associated with an increased risk (OR = 2.2, 95% CI = 1.3–3.6; $P_{trend} = 0.005$). Risk associated with vegetable intake was not statistically significant ($P_{trend} = 0.2$).

Among controls, the distributions of the *XRCC1-399*, *XPD-751*, *MGMT-143*, *MGMT-84* and *XRCC3-241* genotypes were consistent with the Hardy–Weinberg equilibrium, with allelic frequencies similar to those observed in other studies of Caucasians (21,38,39,46,47). None of the polymorphic variants in this series of DNA repair genes was associated with gastric cancer risk (Table II). However, homozygous carriage of the *XRCC1-399* minor allele (*GlnGln*) was associated with increased risk in women (compared with *ArgArg*, OR = 2.3, 95% CI = 1.0–5.1) and decreased risk in men (OR = 0.6, 95% CI = 0.3–1.3). Most of the men in this population were

Table I. Gastric cancer risks associated with smoking and fruit and vegetable intake, Warsaw, Poland, 1994–1997

	Cases (%) $n^b = 281$	Controls (%) $n^b = 390$	OR[a] (95% CI)
Smoking			
Non-smoker	78 (28)	162 (42)	1.0
Pack-years <40	127 (45)	169 (43)	1.7 (1.1–2.4)
Pack-years ≥40	73 (26)	58 (15)	3.1 (1.9–5.1)
P_{trend}			<0.0001
Fruit intake[c]			
High (4th quartile)	34 (15)	89 (23)	1.0
Medium	119 (50)	185 (49)	1.8 (1.1–2.8)
Low (1st quartile)	83 (35)	104 (28)	2.2 (1.3–3.6)
P_{trend}			0.005
Vegetable intake[c]			
High (4th quartile)	50 (21)	89 (24)	1.0
Medium	118 (50)	190 (50)	1.1 (0.7–1.7)
Low (1st quartile)	68 (29)	99 (26)	1.2 (0.8–2.0)
P_{trend}			0.2

[a]All analyses adjusted for age, gender and smoking (unless under assessment); analyses involving fruit and vegetable intake, additionally adjusted for calories from food.
[b]Numbers do not add up to the total because of missing values.
[c]Quartiles defined among control subjects in the full study population: 2.1, 4.9 and 7.0 times a week for fruits and 16.8, 21.0 and 26.6 times a week for vegetables.

Table II. Gastric cancer risks associated with DNA repair polymorphisms, Warsaw, Poland, 1994–1997

Polymorphism	Cases (%) $n^b = 281$	Controls (%) $n^b = 390$	OR[a] (95% CI)
XRCC1 399			
ArgArg	124 (44)	166 (43)	1.0
ArgGln	121 (43)	179 (46)	0.8 (0.6–1.2)
GlnGln	36 (13)	45 (12)	1.0 (0.6–1.7)
P_{trend}			0.7
XPD 751			
LysLys	107 (38)	145 (37)	1.0
LysGln	126 (45)	163 (42)	1.0 (0.7–1.5)
GlnGln	46 (16)	73 (19)	0.8 (0.5–1.2)
P_{trend}			0.4
MGMT 143			
IleIle	216 (77)	310 (79)	1.0
IleVal	61 (22)	73 (19)	1.2 (0.8–1.8)
ValVal	4 (1)	7 (2)	0.7 (0.2–2.6)
P_{trend}			0.6
MGMT 84			
LeuLeu	190 (68)	279 (72)	1.0
LeuPhe	82 (29)	99 (25)	1.2 (0.8–1.7)
PhePhe	8 (3)	9 (2)	1.3 (0.5–3.6)
P_{trend}			0.3
XRCC3 241			
ThrThr	128 (46)	174 (45)	1.0
ThrMet	128 (46)	163 (42)	1.0 (0.7–1.4)
MetMet	25 (8)	53 (14)	0.6 (0.4–1.1)
P_{trend}			0.2

[a]Adjusted for age, gender, and smoking (unless used as a stratifying factor).
[b]Numbers do not add up to the total because of missing value.

smokers (87%), while fewer women smoked (43%); we further evaluated the genotype effects by smoking status.

The increasing gastric cancer risk associated with greater tobacco use (pack-years) was more pronounced among *XRCC1-399 ArgArg* than among *ArgGln* and *GlnGln* carriers ($P_{interaction} = 0.004$, Table III). Similarly, a significant trend of increasing risks associated with recent smoking (i.e. never, former, current smoking) was found only among *XRCC1-399 ArgArg* carriers ($P_{interaction} = 0.0001$, data not shown in Table III). Also, increased risk associated with the *XRCC1-399 Gln* carriers was found only among non-smokers (compared with *ArgArg*, OR = 2.5, 95% CI = 1.4–4.4). Similar patterns of smoking-related risks by genotype subgroups were found for men and women (data not shown). No modification of smoking-related risk was seen with polymorphic variants in genes coding for other DNA repair enzymes.

Gastric cancer risks related to low fruit intake tended to be stronger for carriers of *XPD-751 Gln* or *MGMT-143 Val* and risks related to low vegetable intake tended to be stronger for *XRCC1-399 ArgArg* carriers, but tests for interaction were not statistically significant ($P_{interaction} = 0.1$, 0.2 and 0.1, respectively, Table IV).

Discussion

In this population-based case-control study in Poland, we found no overall effect on gastric cancer risk of non-synonymous polymorphisms in genes coding for selected DNA repair proteins, *XRCC1*, *XPD*, *MGMT*, and *XRCC3*. Risks were greatest, however, in smokers with the *XRCC1-399 ArgArg* genotype. Risks tended to be greater in low fruit consumers who carried the *MGMT-143 ValVal*/*IleVal* or the *XPD-751 GlnGln*/*LysGln* genotypes and in low vegetable consumers who carried the *XRCC1-399 ArgArg* genotypes.

Previous findings for DNA repair polymorphisms and gastric cancer risks were scant and have not been entirely consistent. Unlike our findings, the *XRCC1-399 Gln* variant was associated with a marginally increased risk of gastric cancer in a Chinese population (188 cancer patients), with no apparent risk difference found between smokers and nonsmokers (32). Similar to our findings, the *XRCC1-399* variant was not independently associated with gastric cancer risk in a Korean population (190 cancer patients), but risk pattern by smoking behavior was not evaluated in their study (31). Furthermore, consistent to our data, no association was found for the *XRCC3-241* polymorphism and gastric cancer risk in a Chinese population (188 cancer patients), nor were the risk patterns differed by smoking status (33). Future large epidemiologic studies of gastric cancer are needed to clarify the role of *XRCC1* gene variants and their potential interrelationships with cigarette smoking, evaluated in the context of a better characterized gene haplotype structure (rather than one SNP at a time) for each ethnic group. Smoking-specific and tumor tissue-specific functional patterns in association with a better characterized *XRCC1* haplotype structure also may help clarify our understanding.

No previous studies of gastric cancer have examined the potential interrelationships between DNA repair gene polymorphisms and fruit and vegetable intake. There is substantial evidence that fruit and vegetable intake reduces risk for gastric cancer (26), possibly due to antioxidant activity neutralizing DNA-damaging free radicals and inhibiting formation of N-nitroso compounds (25,26), or through the action of folate and other B vitamins on genetic stability (27). In our data, increased gastric cancer risks associated with low fruit and vegetable intake were somewhat stronger for carriers of *XRCC1-399 ArgArg*, *XPD-751 GlnGln*/*LysGln*, and

Table III. Gastric cancer risks associated with joint effects of DNA repair polymorphisms and smoking, Warsaw, Poland, 1994–1997

Polymorphism	Smoking pack-years OR[a] (95% CI)			
	0	<40	≥40	P_{trend}
XRCC1 399				
ArgArg	1.0	4.4 (2.4–7.9)	5.8 (2.8–12.3)	<0.0001
n: case, control	23, 83	70, 60	31, 22	
GlnGln/ArgGln	2.5 (1.4–4.4)	1.9 (1.1–3.4)	4.8 (2.4–4.5)	0.03
n: case, control	55, 79	57, 109	42, 36	
P	0.002	0.0006	0.7	$P_{interaction} = 0.004$
XPD 751				
LysLys	1.0	2.2 (1.2–4.1)	2.8 (1.3–5.9)	0.004
n: case, control	28, 63	54, 58	25, 24	
GlnGln/LysGln	1.2 (0.7–2.0)	1.6 (0.9–2.8)	3.7 (1.9–7.2)	0.001
n: case, control	50, 96	71, 105	48, 34	
P	0.6	0.1	0.4	$P_{interaction} = 1.0$
MGMT 143				
IleIle	1.0	1.5 (1.0–2.4)	2.9 (1.7–5.0)	0.0001
n: case, control	62, 127	96, 135	56, 47	
ValVal/IleVal	0.9 (0.5–1.8)	2.0 (1.1–3.6)	3.7 (1.6–8.7)	0.02
n: case, control	16, 35	31, 34	17, 11	
P	0.9	0.4	0.8	$P_{interaction} = 0.5$
MGMT 84				
LeuLeu	1.0	1.8 (1.1–2.8)	3.1 (1.7–5.5)	0.0002
n: case, control	53, 118	87, 118	48, 42	
PhePhe/LeuPhe	1.3 (0.7–2.4)	1.8 (1.0–3.1)	4.2 (2.0–8.8)	0.02
n: case, control	24, 41	40, 51	25, 16	
P	0.4	1.0	0.4	$P_{interaction} = 1.0$
XRCC3 241				
ThrThr	1.0	1.7 (1.0–3.0)	2.5 (1.3–4.9)	0.02
n: case, control	39, 77	59, 69	30, 27	
MetMet/ThrMet	1.1 (0.6–1.7)	1.4 (0.8–2.3)	3.6 (1.8–7.1)	<0.0001
n: case, control	39, 85	68, 100	43, 31	
P	0.7	0.3	0.8	$P_{interaction} = 0.5$

[a]Adjusted for age, and gender.

MGMT-143 ValVal/IleVal genotypes. The most promising results for the interrelationships between DNA repair polymorphisms and dietary nutrients were reported previously for other cancer sites. For example, low intake of dietary antioxidants was associated with an increased risk of prostate cancer only among *XRCC1-399 ArgArg* carriers (48). Also, a study of lung cancer (15) reported an increased risk associated with low intake of alpha-tocopherol supplement among *XPD-751 GlnGln/LysGln* carriers. Moreover, an increased risk of lung cancer was found for individuals who consumed low amount of cruciferous and green vegetables and carried the *MGMT-143 Val* allele (49),

A potential limitation of this analysis was the exclusion of cases (39%) and controls (19%) without DNA specimens. Further, a higher percentage of the cases excluded (62%) had advanced stage gastric cancer (i.e. distant metastasis) than the cases included (36%). This, however, was not expected to substantially impact the patterns of our results. First, similar demographic and lifestyle factors were observed among cases and controls with and without DNA samples ($Px^2 > 0.05$), and the allelic frequencies we observed among controls were consistent with those reported for Caucasians by others (21,38,39,46,47). In addition, we obtained similar results including the distant metastasis cases only (data not shown) as opposed to all cases.

There is a likelihood of chance findings for the subgroup analyses. We had low statistical power to detect interactions between genotypes and smoking or fruit and vegetable intake. The inconsistent risk patterns we observed by gender for the *XRCC1-399* variant appeared to be explained by smoking behavior. It is unclear, however, why the *XRCC1-399* variant showed opposite effects for gastric cancer risk between smokers and non-smokers in our data. Data supporting our findings were available from epidemiological (46,50) and functional (51) studies, but there were conflicting results (15,52,53). It is interesting that we found strongest gastric cancer risks for both heavy smokers and low vegetable consumers, who were *XRCC1-399 ArgArg* carriers, perhaps suggesting coordinated mechanisms in play.

In summary, as an attempt to explore the role of DNA repair polymorphisms in various pathways for gastric carcinogenesis, we found no independent effect of the studied DNA repair variants in this population-based case-control study of gastric cancer in Poland. However, we found that smoking-related risk was most profound for carriers homozygous for the *XRCC1-399 Arg* allele, and some evidence that elevated risk related to low fruit or vegetable intake were stronger for carriers of *XRCC1-399 ArgArg*, *XPD-751 GlnGln/LysGln* and *MGMT-143 ValVal/IleVal* genotypes. Although these statistical associations had biological supports, confirmation by further investigations is needed to preclude chance findings. Progress on our understanding of the importance of the DNA repair polymorphisms in gastric carcinogenesis can be advanced by construction of risk-relevant haplotypes considering multiple

Table IV. Gastric cancer risks associated with joint effects of DNA repair polymorphisms and fruit and vegetable intake, Warsaw, Poland, 1994–1997

Polymorphism	Intake of fruits[a] OR[b] (95% CI)				Intake of vegetables[a] OR[b] (95% CI)			
	High (4th quartile)	Medium	Low (1st quartile)	P_{trend}	High (4th quartile)	Medium	Low (1st quartile)	P_{trend}
XRCC1 399								
ArgArg	1.0	1.4 (0.7–2.9)	1.7 (0.8–3.7)	0.3	1.0	1.8 (0.9–3.5)	2.1 (1.0–4.4)	0.07
n: case, control	17, 35	52, 80	38, 46		18, 44	55, 73	34, 44	
GlnGln/ArgGln	0.6 (0.3–1.4)	1.3 (0.7–2.6)	1.6 (0.8–3.3)	0.006	1.5 (0.7–3.2)	1.3 (0.7–2.5)	1.5 (0.7–3.2)	0.9
n: case, control	17, 54	67, 105	45, 58		32, 45	63, 117	34, 55	
P	0.2	0.9	1.0	$P_{interaction} = 0.5$	0.2	0.1	0.4	$P_{interaction} = 0.1$
XPD 751								
LysLys	1.0	1.6 (0.8–3.4)	1.4 (0.6–3.0)	0.6	1.0	0.7 (0.4–1.4)	1.0 (0.5–2.3)	1.0
n: case, control	16, 33	45, 65	27, 42		21, 28	42, 79	25, 33	
GlnGln/LysGln	0.6 (0.3–1.5)	1.4 (0.7–2.8)	2.0 (0.9–4.2)	0.002	0.6 (0.3–1.2)	0.9 (0.5–1.8)	0.9 (0.4–1.9)	0.1
n: case, control	18, 56	74, 114	54, 59		29, 61	75, 105	42, 63	
P	0.3	0.4	0.3	$P_{interaction} = 0.1$	0.1	0.3	0.7	$P_{interaction} = 0.4$
MGMT 143								
IleIle	1.0	1.8 (1.0–3.1)	1.9 (1.1–3.4)	0.06	1.0	1.3 (0.8–2.1)	1.5 (0.8–2.6)	0.2
n: case, control	29, 70	96, 148	59, 83		40, 76	95, 150	49, 75	
ValVal/IleVal	0.8 (0.3–2.4)	1.5 (0.8–3.1)	2.9 (1.4–6.3)	0.04	1.6 (0.6–4.1)	1.2 (0.6–2.2)	1.5 (0.7–3.3)	0.7
n: case, control	5, 19	23, 37	24, 21		10, 13	23, 40	19, 24	
P	0.5	0.5	0.2	$P_{interaction} = 0.2$	0.2	0.8	0.8	$P_{interaction} = 0.6$
MGMT 84								
LeuLeu	1.0	1.4 (0.8–2.4)	1.9 (1.0–3.5)	0.03	1.0	0.9 (0.5–1.5)	1.1 (0.6–2.1)	0.5
n: case, control	26, 61	76, 139	54, 73		38, 63	73, 136	45, 74	
PhePhe/LeuPhe	0.7 (0.3–1.8)	2.4 (1.2–4.5)	2.2 (1.1–4.4)	0.09	0.7 (0.3–1.7)	1.4 (0.8–2.6)	1.6 (0.7–3.3)	0.3
n: case, control	8, 26	43, 45	29, 31		12, 24	45, 53	23, 25	
P	0.5	0.04	0.6	$P_{interaction} = 0.6$	0.3	0.06	0.3	$P_{interaction} = 0.3$
XRCC3 241								
ThrThr	1.0	2.7 (1.3–5.9)	3.0 (1.3–6.7)	0.03	1.0	1.6 (0.9–3.1)	1.6 (0.7–3.3)	0.5
n: case, control	12, 39	55, 78	39, 50		22, 46	56, 77	28, 44	
MetMet/ThrMet	1.6 (0.7–3.7)	2.2 (1.0–4.6)	2.8 (1.3–6.3)	0.07	1.4 (0.7–2.8)	1.2 (0.6–2.2)	1.6 (0.8–3.3)	0.4
n: case, control	22, 50	64, 107	44, 54		28, 43	62, 113	40, 55	
P	0.2	0.4	0.9	$P_{interaction} = 0.5$	0.4	0.2	0.8	$P_{interaction} = 0.7$

[a]Quartiles defined among control subjects in the full study population: 2.1, 4.9 and 7.0 times a week for fruits and 16.8, 21.0 and 26.6 times a week for vegetables.
[b]Adjusted for age, gender, smoking and calories from food.

loci in important genes, replication of findings in large epidemiological studies and sound functional data.

Conflict of Interest Statement: None declared.

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Received November 3, 2004; revised March 18, 2005; accepted March 25, 2005